EXHIBIT 3

Liposomal Bupivacaine

Effective, Cost-effective, or (Just) Costly?

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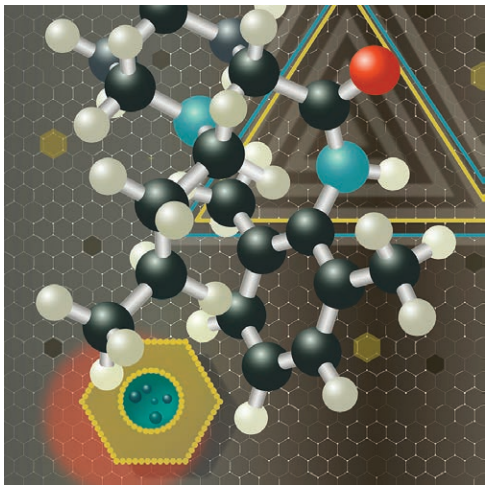
One of the missions of the Food and Drug Administration (Silver Spring, Maryland) is to protect the public health by assuring the safety, efficacy, and security of human drugs.[1] According to Food and Drug Administration guidance, new drugs can be approved as long as they show efficacy compared to placebo, even if there are already drugs approved and available that have been deemed effective.[2] Exparel (Pacira Biosciences, Inc., USA), an extended release liposomal formulation of bupivacaine, first approved by the Food and Drug Administration in 2011 for surgical site infiltration, was approved under these circumstances. In this issue, two articles review 10 yr of research on the clinical effectiveness of liposomal bupivacaine. Ilfeld *et al.*[3] provide an extensive narrative review of published randomized controlled trials, and Hussain *et al.*[4] conducted a systemic review and meta-analysis of the clinical effectiveness of liposomal *versus* nonliposomal bupivacaine for peripheral nerve blocks.



"…liposomal bupivacaine was found to be superior to comparators in 46% of… conflicted [pharma-sponsored] trials but was found to be superior in only 11% of the nonconflicted trials."

The narrative review by Ilfeld *et al.* included 76 randomized controlled trials. Importantly, they were evaluated using the Cochrane Risk of Bias Version 2 tool. This tool consists of five domains: bias from the randomizing process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of outcome, and bias in selection of reported results. It does not measure the conduct of a trial. A summary bias judgment can be either "low" or "high" risk of bias, or can express "some concerns," and a high risk summary judgment generally indicates a finding of high risk in at least one of the domains.[5] The authors found that 35 to 40% of randomized controlled trials reviewed had evidence of high risk or some concerns for bias. The chief sources of bias included lack of trial registration, registration after enrollment, failure to define the primary outcome measure, and problems with definition (*e.g.*, discrepancy between registry and published article). Minimization of bias in randomized controlled trials is important to prevent data distortion and erroneous conclusions. The Cochrane Risk of Bias tool does not measure conflicts of interest by industry funding. Almost half of the studies in this review reported either direct funding or financial support for the authors by the manufacturer of liposomal bupivacaine. Not surprisingly, liposomal bupivacaine was found to be superior to comparators in 46% of these conflicted trials but was found to be superior in only 11% of the nonconflicted trials.

The primary outcome in these 76 trials varied and was not always designated. There were two types of primary outcome measures used: postoperative pain scales such as the visual analogue scale scores and numeric rating scales scores, or the mean morphine equivalents administered postoperatively to "rescue" the patient from pain. Some studies reported mean values, and others reported area under the curve values.

The first 12 studies reviewed compared liposomal bupivacaine surgical site infiltration to placebo. Seven found no statistical difference between liposomal bupivacaine and placebo, and of these, 88% were deemed at low risk for bias. The five that did show statistical differences were all rated with high risk for bias. Thirty-six of the randomized controlled trials compared surgical site infiltration of liposomal bupivacaine to surgical site infiltration of bupivacaine, ropivacaine, or lidocaine. Twenty-seven of these comparisons

Image: A. Johnson, Vivo Visuals.

This editorial accompanies the articles on pp. 147 and 283.

Accepted for publication December 1, 2020. From Harvard Medical School, Cambridge, Massachusetts, and Boston Children's Hospital, Boston, Massachusetts.

 Anesthesiology 2021; 134:139–42. DOI: 10.1097/ALN.0000000000003658

<zdoi;. DOI: 10.1097/ALN.0000000000003658>

used a maximum dose of liposomal bupivacaine of 266 mg but used a smaller dose of regular bupivacaine or ropivacaine, possibly biasing the studies toward results favoring liposomal bupivacaine. Only six of the 36 studies of comparing surgical site infiltration with liposomal bupivacaine with nonliposomal local anesthetic infiltration found the liposomal preparation to be superior. Five of these six studies were judged to have high or concerning risk for bias. In five of the six studies, the active comparator dose of bupivacaine was much lower than the liposomal bupivacaine dose, demonstrating that more bupivacaine works better than less bupivacaine. Twelve studies compared liposomal bupivacaine for surgical infiltration with a peripheral nerve block administered with either nonliposomal bupivacaine or ropivacaine. The final group of 16 studies evaluated liposomal bupivacaine for a nerve block or epidural injection compared to placebo or active comparators, nonliposomal bupivacaine, or intrathecal hydromorphone, using the similar outcome measures to all the previous trials. Of these last 28 trials reviewed, 43% showed superiority of liposomal bupivacaine; 82% showed high risk or some concerns for bias. The authors concluded, "Whether introduced by surgical infiltration or as part of a peripheral nerve block, the preponderance of current evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics when treating postoperative pain."

The systematic review and meta-analysis by Hussain *et al.* of the clinical effectiveness of liposomal *versus* nonliposomal bupivacaine for peripheral nerve blocks evaluated the primary outcome of the 24- to 72-h difference in the weighted mean area under the curve rest pain scores between patients receiving perineural analgesia inclusive of liposomal bupivacaine *versus* nonliposomal local anesthetics. The authors chose this time frame for the primary outcome measure because liposomal bupivacaine is promoted to improve the duration and quality of analgesia beyond the first 24 h.[4] A variety of secondary outcomes relating to postoperative pain rating scores and opioid rescues were also evaluated during the postoperative period of 0 to 72 h. Nine trials were included in this meta-analysis. The authors found that the mean difference (95% CI) in area under the curve of rest pain was found to be 1.0 cm/h (0.5 to 1.6; $P = 0.003$) in favor of liposomal bupivacaine, but this difference failed to meet the predefined threshold for clinical significance (*i.e.*, 2.0 cm/h; $P < 0.001$). Liposomal bupivacaine was similar to nonliposomal bupivacaine for all other analgesic and functional outcomes. The authors concluded that liposomal bupivacaine used perineurally in peripheral nerve blocks provides a clinically unimportant improvement in the area under the curve of postoperative pain scores compared to nonliposomal bupivacaine.

The results of these two articles should not come as a surprise in light of the early studies performed for the regulatory approval of liposomal bupivacaine. In 2006, SkyePharma, later known as Pacira Pharmaceuticals and then Pacira Biosciences, collectively referred to here as Pacira Biosciences, submitted an New Drug Application application to the Food and Drug Administration for Exparel brand liposomal bupivacaine for an indication of relief of postoperative surgical pain, administered as wound infiltration.[6] For this indication, Pacira submitted five phase 2 active comparator-controlled studies and three phase 3 active comparator-controlled studies using nonliposomal bupivacaine as the comparator.[6] None of these eight studies showed clinical or statistical difference between the two formulations.

Unable to demonstrate a benefit over nonliposomal bupivacaine, in 2009, the sponsor submitted two phase 3 placebo-controlled clinical trials showing efficacy of liposomal bupivacaine against placebo.[6] As allowed by regulation, despite no greater efficacy of liposomal bupivacaine than nonliposomal bupivacaine, the Food and Drug Administration in 2011 approved liposomal bupivacaine for surgical site infiltration to relieve postoperative pain for hemorrhoidectomy and bunionectomy. For this initial approval, the Food and Drug Administration deemed it not necessary for an advisory committee to meet.[7]

In 2014, Pacira submitted a supplemental New Drug Application application for approval of liposomal bupivacaine for an additional indication of postsurgical analgesia *via* nerve block, for which they submitted data from two new studies. The first investigated intercostal nerve blocks and found that liposomal bupivacaine was not superior to placebo, based on no differences in area under the curve analysis for pain intensity at rest using a numerical rating scale-R over 72 h. The second investigated femoral nerve blocks and found that liposomal bupivacaine at a dose of 266 mg was superior to placebo for pain relief, based on a primary outcome measure of area under the curve analysis of Numeric Rating Scale-Rest through 72 h but not superior on its secondary outcome measure of time to first opioid rescue. This supplemental New Drug Application was not approved in the first review cycle. In 2017, Pacira submitted two new multicenter, randomized, double-blind, and placebo-controlled nerve block studies.[8,9] The first evaluated the efficacy of liposomal bupivacaine for postsurgical analgesia *via* femoral nerve block in patients undergoing total knee arthroplasty. The second evaluated liposomal bupivacaine for postsurgical analgesia *via* ultrasound-guided brachial plexus nerve blocks by either supraclavicular or interscalene approach in patients undergoing shoulder surgery. Out of these four studies, both the two in 2014 and the two in 2017, the brachial plexus nerve block study was the only one that met both the primary efficacy endpoint of improved area under the curve estimates of pain relief for the first 48 to 72 h after surgery and decreased opioid rescues.

The Food and Drug Administration Anesthetic and Drug Products Advisory Committee met in 2018

to review the supplemental New Drug Application request to approve liposomal bupivacaine for the new indication of regional nerve blocks.[10,11] This advisory committee consisted of 10 members with expertise in anesthesiology, pain medicine, pharmacology, or biostatistics, as well as a consumer and industry representative. Concerns raised by this committee included the lack of active comparator groups in the submitted studies, a lack of safety studies, and the lack of evidence for opioid sparing. Most of the voting advisory committee members voted six to four against expanding the indication for liposomal bupivacaine. In 2018, the Food and Drug Administration approved Exparel for "…use as an interscalene brachial plexus nerve block to produce post-surgical regional analgesia following shoulder surgery in adults."[12]

To summarize, both the review by Ilfeld *et al.* and the meta-analysis by Hussain *et al.* concluded that liposomal bupivacaine did not show clinical superiority over existing, active comparators, nonliposomal bupivacaine or ropivacaine. For the indication for infiltration, the studies submitted by Pacira Biosciences did not demonstrate superiority of liposomal bupivacaine compared to these same active comparators. For the indication of peripheral nerve block, they submitted only placebo studies. Although demonstrating efficacy of a new agent is simplest using a randomized placebo-controlled trial design, this design gives no information about the efficacy of a new agent compared to existing agents. Trials that have an active comparator arm as well as a placebo arm can determine efficacy as well as give information about efficacy *vis-à-vis* existing, effective drugs.

Why is all of this important? New drugs can be very financially rewarding for pharmaceutical companies.[13] Once Exparel was approved, Pacira Biosciences began an aggressive and powerful marketing strategy. Between 2013 and 2019, they paid $25.8 million to more than 27,000 physicians for a variety of services including compensation for being a speaker or faculty at nonaccredited educational events.[14] Sales of liposomal bupivacaine increased during this time with the company reporting a 25% growth in 2019 over 2018 with full-year revenues of $421 million in 2019.[15] The cost of a single dose of 266 mg of Exparel brand liposomal bupivacaine is about $334.[16] Nonliposomal bupivacaine costs about $3 per dose. In this era of medical austerity, when the benefits and costs of expensive drugs are being considered, one would hope that newly approved expensive drugs would at least be an improvement over existing, inexpensive drugs.

Competing Interests

The author declares no competing interests. The author was the acting Chair for the Food and Drug Administration Anesthetic and Analgesic Drug Products Advisory Committee February 14 and 15, 2018, which advised on Pacira's (Pacira Biosciences, Parsippany, New Jersey) sNDA application for expanded indication for Exparel for nerve blocks.

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References

1. Food and Drug Administration: What we do. 2018. Available at: https://www.fda.gov/about-fda/what-we-do. Accessed November 5, 2020.
2. US Food and Drug Adnimistration: CFR - Code of Federal Regulations Title 21. April 1, 2019. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126. Accessed November 11, 2020.
3. Ilfeld BM, Eisenach JC, Gabriel RA: Clinical effectiveness of liposomal bupivacaine administered by infiltration or peripheral nerve block to treat postoperative pain: A narrative review. Anesthesiology 2020; 134:283–344
4. Hussain N, Brull R, Sheehy B, Essandoh MK, Stahl DL, Weaver TE, Abdallah FW: Perineural liposomal bupivacaine is not superior to nonliposomal bupivacaine for peripheral nerve block analgesia: A systematic review and meta-analysis. Anesthesiology 2020; 134:147–64
5. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366:l4898
6. Food and Drug Administration: NDA 022496, S009, EXPAREL assessment of efficacy data of studies submitted in support of sNDA. February 15, 2017. Available at: https://www.fda.gov/media/111376/download. Accessed November 20, 2020.
7. Center for Drug Evaluation and Research: Application number: 022496 Orig1s000, Cross Discipline Team Leader Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig-1s000MedR.pdf. Accessed November 5, 2020.
8. Food and Drug Administration: Briefing document anesthesia and analgesia drug products advisory meeting February 14 and February 15, 2018. Available at: https://www.fda.gov/media/110968/download. Accessed November 4, 2020.
9. Food and Drug Administration: Advisory Committee Meeting briefing document, EXPAREL® (bupivacaine liposome injectable suspension). Meeting of the Anesthetic and Analgesic Drug Products

Advisory Committee. Available at: https://www.fda.gov/files/advisory%20committees/published/Pacira-Briefing-Information-for-the-February-14-15--2018-Meeting-of-the-Anesthetic-and-Analgesic-Drug-Products-Advisory-Committee.pdf. Accessed November 5, 2020.

10. Litman RS: Anesthetic and Analgesic Drug Products Advisory Committee activity and decisions in the opioid-crisis era. Anesthesiology 2020; 133:740–9
11. Food and Drug Administration: Center for Drug Evaluation and Research, summary minutes of the Anesthetic and Analgesic Drug Products Advisory Committee meeting, February 14-15, 2018. Available at: https://www.fda.gov/media/112187/download. Accessed November 4, 2020.
12. Food and Drug Administration: In brief: FDA approves new use of Exparel for nerve block pain relief following shoulder surgeries. April 16, 2018. Available at: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-approves-new-use-exparel-nerve-block-pain-relief-following-shoulder-surgeries. Accessed November 5, 2020.
13. Van Zee A: The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. Am J Public Health 2009; 99:221–7
14. OpenPaymentsData.CMS.gov: Pacira Pharmaceuticals Incorporated. 2020. Available at: https://openpaymentsdata.cms.gov/company/100000000135. Accessed November 5, 2020.
15. Pacira Biosciences, Inc.: News release Pacira reports record fourth quarter and full-year revenues. 2020. Available at: https://investor.pacira.com/news-releases/news-release-details/pacira-reports-record-fourth-quarter-and-full-year-revenues-0. Accessed November 5, 2020.
16. Exparel: EXPAREL is a cost-effective option for postsurgical pain management in the hospital and ambulatory (outpatient) settings. 2020. Available at: https://www.exparel.com/hcp/value/total-hip-arthroplasty. Accessed November 6, 2020.